35. (Amended) The method of Claim 34, wherein the tumor necrosis factor related disease is selected from the group consisting of: an autoimmune disease, an inflammatory bowel disease, a bacterial infection, a viral infection, a parasitic infection, a malignancy, and a neurodegenerative disease.

36. (Amended) The method of Claim 35, wherein the TNF related disease is selected from the group consisting of: rheumatoid arthritis, septic shock, cerebral malaria, inflammatory bowel disease, multiple sclerosis, allograft rejection, host versus graft disease, neoplastic pathology and endotoxemic response.

37. (Amended) The method of Claim 34, wherein the tumor necrosis factor related disease is rheumatoid arthritis.

REMARKS

Claims 1-3, 6, 8, 14-17 and 19-37 are pending and under examination in the subject application. Applicants have amended claims 1, 2, 6, 14-16, 19-23, 27-29, 31 and 33-37 in order to introduce certain format changes. Support for the linker length of from about 10 to about 30 amino acid residues can be found in the specification at, *inter alia*, page 7, line 15. The remaining amendments address additional format issues. Applicants maintain that these amendments raise no issue of new matter, and respectfully request entry of this Amendment. Upon entry of this Amendment, claims 1-3, 6, 8, 14-17 and 19-37 will still be pending and under examination.

Pursuant to the requirements of 37 C.F.R. 1.121(c)(1)(ii),

applicants annex hereto as Exhibit A claims 1, 2, 6, 14-16, 19-23, 27-29, 31 and 33-37 marked up to show the changes made herein relative to the previous version of those claims.

In view of the arguments set forth below, applicants maintain that the Examiner's objections and rejections made in the June 15, 2001 Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw same.

The Claimed Invention

This invention provides a small molecular weight tumor necrosis factor receptor-based molecule and related methods. This molecule binds TNF and comprises all or a functional portion of at least two extracellular domains of TNF receptors linked via one or more polypeptide linkers. The polypeptide linkers are from about 10 to about 30 amino acids in length.

The claimed molecule shows *surprising* advantages over other multi-TNF receptor-based molecules. Specifically, the instant molecule, as exemplified by Hu TNF-R75 ECD, shows the same anti-TNF specific activity as an Ig-based TNF receptor molecule - and at *only a third of the concentration* required for the Ig-based molecule. Even more dramatic is the fact that a concentration of TNF receptor monomer 300-fold higher than that tested for the instant molecule *was ineffective* against the effects of TNF.

The claimed molecule is characterized by a low molecular weight, an optimal linker length, and the absence of an Ig Fc domain which has

the potential to cause side effects. These features combined make this molecule unexpectedly superior to known TNF receptor-based molecules.

Rejection Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 20-23 and 34-37 under 35 U.S.C. §112, first paragraph, as allegedly not enabled and allegedly lacking proper written description.

Specifically, the Examiner asserted that the specification does not reasonably provide enablement or written description for a method of preventing a tumor necrosis factor-related disease.

In response, applicants respectfully traverse the Examiner's rejection, pointing out that the language objected to by the Examiner does not appear in claims 20-23 and 34-37 as amended.

In view of the above remarks, applicants maintain that claims 20-23 and 34-37 satisfy the requirements of 35 U.S.C. §112, first paragraph.

Rejections Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 19-23 and 33-37 under 35 U.S.C. §112, second paragraph, as allegedly unclear. Specifically, the Examiner maintains as indefinite the claim language "host".

In response, applicants respectfully traverse the Examiner's

rejection, pointing out that the term "subject", and not "host", appears in claims 19-23 and 33-37 as amended.

The Examiner also rejected claim 27 under 35 U.S.C. §112, second paragraph, maintaining as indefinite the claim language "wherein the tumor necrosis factor is of human origin".

In response, applicants respectfully traverse the Examiner's rejection, pointing out that the language "wherein the tumor necrosis factor receptors are of human origin", and not the language objected to by the Examiner, appears in claim 27 as amended.

Further, the Examiner rejected claim 29 under 35 U.S.C. §112, second paragraph, alleging that the claim is indefinite because as written, it is not clear if the entire receptor molecule or just the polypeptide linker comprises SEQ ID NO:2.

In response, applicants respectfully traverse the Examiner's rejection, pointing out that the rejected claim, as amended, makes clear that the receptor molecule comprises SEQ ID NO:2.

In view of the above remarks, applicants maintain that claims 19-23, 27, 29 and 33-37 satisfy the requirements of 35 U.S.C. §112, second paragraph.

Rejection Under 35 U.S.C. §103(a)

The Examiner rejected claims 1-3, 6, 8, 14-17 and 19-37 under 35

U.S.C. §103(a) as allegedly unpatentable over Wallach, et al. (U.S. Patent No. 5,478,925, "Wallach I") or Wallach, et al. (EP 0 526 905, "Wallach II").

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

Again, claims 1-3, 6, 8, 14-17 and 19-37 provide a small molecular weight TNF receptor-based molecule and methods of using same. This molecule binds TNF and comprises all or a functional portion of two extracellular domains of TNF receptors linked via one or more polypeptide linkers of about 10 to about 30 amino acid residues in length.

As stated already, the claimed molecule is characterized by a low molecular weight, an optimal linker length, and the absence of an Ig Fc domain which has the potential to cause side effects. These features combined make this molecule unexpectedly superior to known TNF receptor-based molecules.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First the cited references, when combined, must teach or suggest every element of the claims. Second, one of ordinary skill must have been motivated to combine the teachings of the cited references at the time of the invention. Third, there must be a reasonable expectation that the claimed invention would succeed.

Here, each of the cited references fails to support a *prima facie* case of obviousness. Specifically, to support a *prima facie* case of obviousness, each of Wallach I and Wallach II, in view of routine skill in the art, would have to teach or suggest every element of the claims.

Neither Wallach I nor Wallach II does this.

Specifically, each reference teaches TNF receptor multimers. These multimers are made from monomers held together by *any* means (see Wallach II, page 2, lines 44-46). For example, the monomers may be held together by both covalent bonding such as via chemical cross-linkers, as well as non-covalent bonding such as via liposome formation. Joining monomers covalently via a peptide linker is but only one method out of a *veritable universe of possibilities* taught by the references. Moreover, neither reference teaches or suggests the instant polypeptide linkers of from about 10 to about 30 amino acid residues. This element is not provided by routine skill either. In sum, each reference, when combined with routine skill, fails to teach all elements of the claims.

Moreover, when combined with routine skill, Wallach I and II also fail to provide a reasonable expectation of success. These references offer no experimental evidence demonstrating the success of their claimed multimers. They also fail to give guidance as to how one would arrive at a linker length which would provide the unexpected advantages seen with the instant molecule. Thus, neither reference provides a reasonable expectation of success and, indeed, creates at best an invitation to experiment further.

In light of these teachings and their shortcomings, the Examiner has failed to show how either cited reference teaches or suggests every element of the claims, or provides a reasonable expectation of success for the claimed invention. To maintain otherwise would be hindsight.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 1-3, 6, 8, 14-17 and 19-37 over Wallach I or II, in view of routine skill in the art at the time of the invention. For the same reasons, applicants alternatively maintain that the rejected claims would not have been obvious over these references.

The Examiner also rejected claims 1-3, 6, 8, 14-17 and 19-37 under 35 U.S.C. §103(a) as allegedly unpatentable over Smith, et al. (U.S. Patent No. 5,395,760).

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

The rejected claims are discussed above.

Smith, et al. teach that "both monovalent and polyvalent forms of TNF-R are useful in the compositions and methods of the invention...[f]or example, a bivalent soluble TNF-R may consist of two tandem repeats of amino acids 1-235 of FIG. 2A, separated by a linker region" (column 10, lines 33-39). In essence, Smith, et al. teach what Wallach I and II teach: a receptor-based molecule with a virtually infinite number of structural permutations. In

combination with routine skill in the art, Smith, et al. do *not* teach or suggest a receptor-based molecule comprising a *peptide* linker of a *defined* length, as in the claimed invention. Thus, this reference fails to teach or suggest all elements of the rejected claims, and fails to provide a reasonable expectation of success.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 1-3, 6, 8, 14-17 and 19-37 over Smith, et al., in view of routine skill in the art at the time of the invention. For the same reasons, applicants alternatively maintain that the rejected claims would not have been obvious over this reference.

In view of the above remarks, applicants maintain that claims 1-3, 6, 8, 14-17 and 19-37 satisfy the requirements of 35 U.S.C. §103(a).

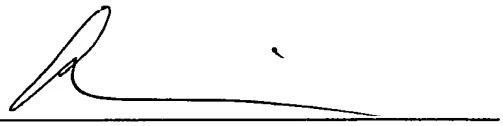
Summary

In view of the amendments and remarks made herein, applicants maintain that the claims pending in this application are in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the $110.00 fee for an additional one-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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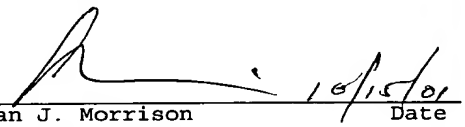

10/15/01

Alan J. Morrison
Reg. No. 37,399

Date

Exhibit A

Marked-Up Version of Amended Claims

1. (Thrice amended) A receptor molecule which binds to tumor necrosis factor comprising all or a functional portion of two extracellular domains of tumor necrosis factor receptors linked to a polypeptide linker, wherein said polypeptide linker is from about 10 to about 30 amino acid residues in length and is covalently bonded to said extracellular domains via peptide bonds, and wherein the receptor molecule is capable of binding to a tumor necrosis factor trimer in a stoichiometric ratio of almost 1:1.

2. (Twice amended) The receptor molecule of Claim 1, wherein the extracellular domains are selected from the group consisting of: the extracellular domain of a p75 tumor necrosis factor receptor and the extracellular domain of a p55 tumor necrosis factor receptor or functional portions thereof.

6. (Twice amended) The receptor molecule of Claim 2, wherein the extracellular domains of the tumor necrosis factor receptors are the same.

14. (Twice amended) Isolated DNA comprising a receptor molecule which binds to tumor necrosis factor comprising all or a functional portion of two extracellular domains of tumor necrosis factor receptors linked to a polypeptide linker, wherein said polypeptide linker is from about 10 to about 30 amino acid residues in length and is covalently bonded to said extracellular domains via peptide bonds, and wherein the DNA comprises SEQ ID NO:1.

15. (Thrice amended) A method of making a construct which

expresses a receptor molecule which binds to tumor necrosis factor comprising all or a functional portion of the extracellular domain of two or more tumor necrosis factor receptors linked to a polypeptide linker from about 10 to about 30 amino acid residues in length, wherein the receptor molecule is capable of binding to a tumor necrosis factor trimer in a stoichiometric ratio of almost 1:1, comprising the steps of:

a) obtaining a first vector which expresses all or a functional portion of an extracellular domain of a first tumor necrosis factor receptor and a signal peptide of a secreted protein;

b) obtaining a second vector which expresses all or a functional portion of an extracellular domain of a second tumor necrosis factor receptor; and

c) ligating the first vector of (a) to the second vector of (b) using a coding sequence for a polypeptide linker

so that the first vector of (a) is linked to the second vector of (b) using the coding sequence for the polypeptide linker resulting in a construct which expresses all or a functional portion of the extracellular domain of the first tumor necrosis factor receptor and all or a portion of the extracellular domain of the second tumor necrosis factor receptor linked using the polypeptide linker.

16. (Twice amended) The method of Claim 15 further comprising the steps of:

a) obtaining a first vector which codes for all or a functional portion of an extracellular domain of a first tumor necrosis factor receptor and signal peptide of a secreted protein linked to all or a functional portion of an extracellular domain of a second tumor necrosis factor

receptor using a coding sequence for a polypeptide linker;

b) obtaining a second vector which codes for all or a functional portion of an extracellular domain of a third tumor necrosis factor receptor; and

c) ligating the first vector of (a) to the second vector of (b) using a coding sequence for a polypeptide linker so that the first vector of (a) is linked to the second vector of (b) using the coding sequence for a polypeptide linker resulting in a construct which expresses all or a functional portion of the extracellular domain of the first tumor necrosis factor receptor and all or a portion of the extracellular domain of the second tumor necrosis factor receptor and all or a portion of the extracellular domain of the third tumor necrosis factor receptor all being linked using the first and second polypeptide linkers.

19. (Twice amended) A method of inhibiting the biological activity of tumor necrosis factor comprising administering to a [host] subject a TNF-inhibiting amount of a receptor molecule according to Claim 1.

20. (Twice amended) A method of treating [or preventing] a tumor necrosis factor related disease in a [host] subject in need thereof comprising administering to the [host] subject a TNF-inhibiting amount of a receptor molecule according to Claim 1.

21. (Amended) [A] The method of Claim 20, wherein the tumor necrosis factor related disease is selected from the group consisting of: an autoimmune disease, an inflammatory bowel disease, a bacterial infection, a viral infection, a parasitic

infection, a malignancy, and a neurodegenerative disease.

22. (Amended) [A] The method of Claim 21, wherein the TNF related disease is selected from the group consisting of: rheumatoid arthritis, septic shock, cerebral malaria, inflammatory bowel disease, multiple sclerosis, allograft rejection, host versus graft disease, neoplastic pathology and endotoxemic response.

23. (Amended) [A] The method of Claim 20, wherein the tumor necrosis factor related disease is rheumatoid arthritis.

27. (Amended) The receptor molecule of Claim 1, wherein the tumor necrosis [is] factor receptors are of human origin and the polylinker is a polyglycine linker sequence.

28. (Amended) Isolated DNA comprising a sequence encoding a receptor molecule which binds to tumor necrosis factor comprising all or a functional portion of two extracellular domains of tumor necrosis factor receptors linked to a polypeptide linker from about 10 to about 30 amino acid residues in length, wherein said polypeptide linker is covalently bonded to said extracellular domains via peptide bonds and wherein the DNA encodes the amino acid sequence of SEQ ID NO:2.

29. (Amended) A receptor molecule which binds to tumor necrosis factor comprising all or a functional portion of two extracellular domains of tumor necrosis factor receptors linked to a polypeptide linker, wherein the molecule comprises the amino acid sequence of [comprising] SEQ ID NO:2.

31. (Amended) The method of Claim 30 further comprising the steps

of:

a) obtaining a first vector which codes for all or a functional portion of an extracellular domain of a first tumor necrosis factor receptor and signal peptide of a secreted protein linked to all or a functional portion of an extracellular domain of a second tumor necrosis factor receptor using a coding sequence for a polypeptide linker;

b) obtaining a second vector which codes for all or a functional portion of an extracellular domain of a third tumor necrosis factor receptor; and

c) ligating the first vector of (a) to the second vector of (b) using a coding sequence for a polypeptide linker so that the first vector of (a) is linked to the second vector of (b) using the coding sequence for a polypeptide linker resulting in a construct which expresses all or a functional portion of the extracellular domain of the first tumor necrosis factor receptor and all or a portion of the extracellular domain of the second tumor necrosis factor receptor and all or a portion of the extracellular domain of the third tumor necrosis factor receptor all being linked using the first and second polypeptide linkers.

33. (Amended) A method of inhibiting the biological activity of tumor necrosis factor comprising administering to a [host] subject a TNF-inhibiting amount of a receptor molecule encoded by the DNA of Claim 28.

34. (Amended) A method of treating [or preventing] a tumor necrosis factor related disease in a [host] subject in need thereof comprising administering to the [host] subject a TNF-

inhibiting amount of a receptor molecule encoded by the DNA of Claim 28.

35. (Amended) [A] The method of Claim 34, wherein the tumor necrosis factor related disease is selected from the group consisting of: an autoimmune disease, an inflammatory bowel disease, a bacterial infection, a viral infection, a parasitic infection, a malignancy, and a neurodegenerative disease.

36. (Amended) [A] The method of Claim 35, wherein the TNF related disease is selected from the group consisting of: rheumatoid arthritis, septic shock, cerebral malaria, inflammatory bowel disease, multiple sclerosis, allograft rejection, host versus graft disease, neoplastic pathology and endotoxemic response.

37. (Amended) [A] The method of Claim 34, wherein the tumor necrosis factor related disease is rheumatoid arthritis.